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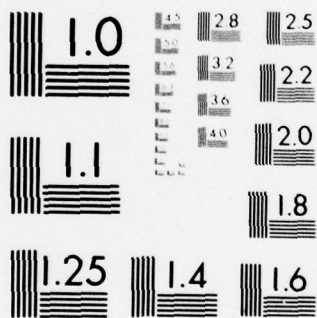
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NO. 497 ✓

THE EFFICACY OF THERAPY AT DOSES SUGGESTED FOR
SELF-AID AGAINST GD POISONING (U)

by

J.A. Lipp

PROJECT NO. 13D30



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ABSTRACT

Monkeys were exposed to 1 LD₅₀ of GD and treated with a combination of clonazepam, atropine and toxogonin at doses suggested for self-aid. The doses used were based on equivalent human doses of 2 mg/man of atropine, 5 mg/man of clonazepam and 280 mg/man of toxogonin. This therapy, given by intramuscular injection when the initial signs of poisoning occurred, adequately suppressed the abnormal EEG and muscular activity. Atropine reversed cardiac arrhythmia, but the GD-induced respiratory depression and bradycardia appeared more resistant and in some animals additional atropine was necessary. Control animals that only received therapy did not appear to be incapacitated. The results of this study suggest that this therapy would produce a degree of protection against GD poisoning and could be used as self-aid.

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INTRODUCTION

It has been reported that the drug combination of clonazepam and atropine is an effective therapy for GD poisoning (1,2). The minimal effective dose was 0.07 mg/kg of clonazepam and 0.25 mg/kg of atropine (2). The side effects of a drug must be considered when determining the dose to be used in a therapeutic regime; however, circumstances dictate the severity of side effects that can be tolerated. Thus, the dose used to treat an individual exposed to GD must be sufficient to counteract the fatal effects even though the side effects of the drugs may be debilitating; whereas the dose of therapy used in only suspected cases of exposure to GD should not induce intolerable side effects. The dose used in previous studies (2) would possibly induce some debilitation (especially the dose of atropine) and should not be used in cases of only suspected poisoning.

The object of this study is to determine if a dose of clonazepam and atropine can be used which will not induce incompatible side

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effects yet produce a degree of protection against GD poisoning. It was decided to use atropine at a dose of 0.03 mg/kg which is equivalent to 2 mg per 70 kg/man, the usual clinical dose, and clonazepam at 0.07 mg/kg which is equivalent to 5 mg per 80 kg/man. Previous studies have reported that this dose of clonazepam is effective; however, the effectiveness of the proposed dose of atropine is unknown.

PROCEDURE

The procedure used in this study has been described in detail in previous studies (1,2). Briefly, nine monkeys with chronic implanted cerebral electrodes were used. Control EEG, respiratory and heart rates were obtained. EEG, respiratory and heart rate recordings began immediately following the injection of GD and continued throughout the experiment. GD was diluted with 0.9% saline and injected into the thigh of the monkey at a dose of 7 - 8 μ g/kg. When the animal began to exhibit the initial signs of GD poisoning which include oral movements, peripheral tremor and synchronization of the EEG pattern, therapy which consisted of clonazepam (0.07 mg/kg), atropine (0.03 mg/kg), and toxogonin (4.0 mg/kg) was administered by IV injection into the brachial vein. Additional atropine was given to any animal that exhibited severe dyspnea after receiving the initial therapy. All animals were placed in their respective holding cages within 2 hours of receiving GD and observed for the remainder of the day.

Three monkeys were given the therapy without receiving GD and the above mentioned physiological activity recorded.

RESULTS

All animals exposed to GD exhibited some symptoms of poisoning, which included changes in the EEG pattern (Fig. 1-B, 2-B), alterations in the respiratory pattern (Fig. 2-B) and changes in cardiac activity (Fig. 1-B) or apnea. It should be noted that the dose of GD used in this study was about 1 LD₅₀.

Following administration of therapy, the animals appeared alert,

but quiet, exhibiting no abnormal movements. The EEG exhibited desynchronized sharp wave activity characteristic of clonazepam (Fig. 1-D, 2-C). The cardiac arrhythmia exhibited by one monkey immediately disappeared (Fig. 1-C) and respiration became synchronous (Fig. 1-D, 2-D).

The heart rate in all animals showed a significant decrease while the respiratory rate increased. Two monkeys had to be given additional atropine and they continued to exhibit dyspnea and bradycardia (Fig. 3-D). Within one hour of receiving GD, the average heart rate had decreased 59% while respirations had increased 49% (Fig. 4).

All animals were lethargic and exhibited some ataxia when placed in the holding cages, but were capable of maintaining an upright posture within one hour.

The control animals, that received therapy only, did not exhibit any significant changes in behavior or EEG activity. One exhibited a small decrease in heart rate (20%) which occurred within five minutes of receiving the drugs.

DISCUSSION

The results of this experiment showed that the dose of therapy used in this study provided some protection to animals exposed to 1 LD₅₀ of GD. The effectiveness of clonazepam in suppressing seizure activity and abnormal movements had been confirmed in other studies. The peripheral effects of atropine were more evident than the central action. Administration of atropine immediately reversed the cardiac arrhythmia, whereas the GD-induced respiratory depression remained evident and some animals required additional atropine. Consequently the dose of atropine (2 mg/70 kg) could be considered as the minimal effective dose and any reduction in the dose would possibly negate the efficacy of atropine.

Administration of therapy to control animals did not appear to affect their normal behavior which may indicate that an equivalent dose may not interfere with the normal function of a human. This should be

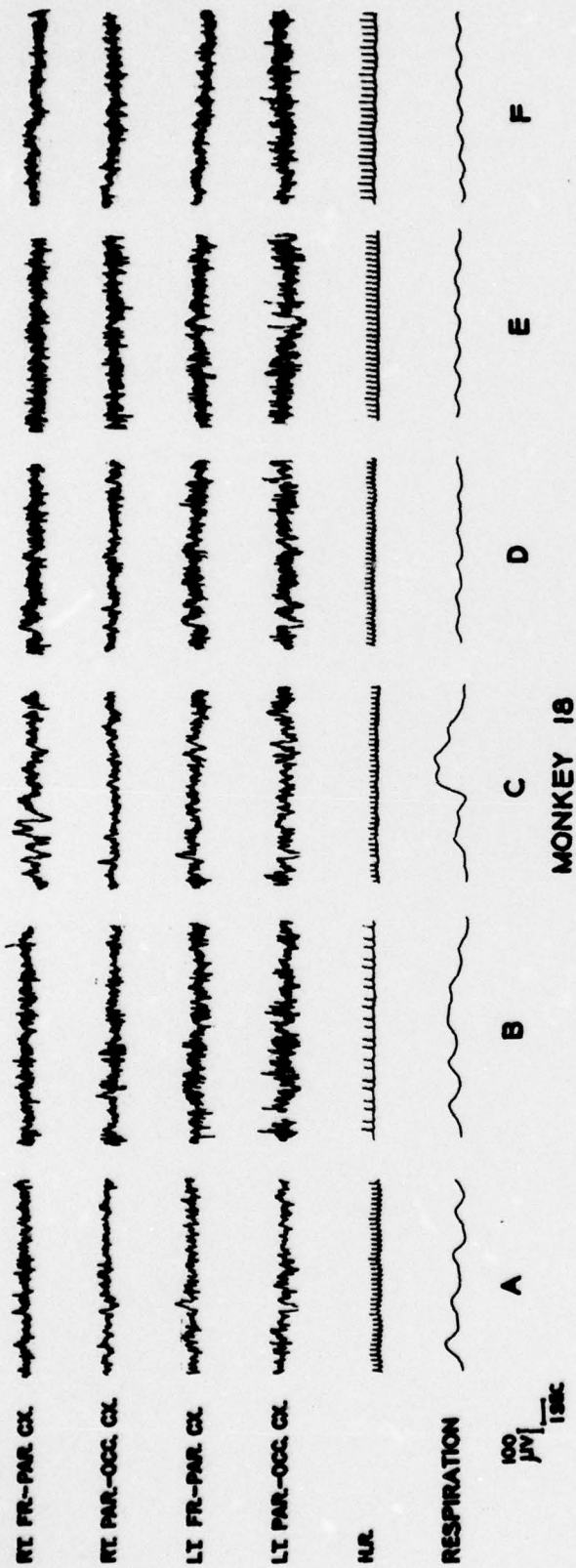
confirmed by human clinical trial.

Therefore, the results of this study suggest that therapy consisting of atropine (2 mg/70 kg), clonazepam (5 mg/70 kg) and toxogonin (280 mg/70 kg) would produce a degree of protection against GD poisoning yet not interfere with the normal behavior, and may be considered for self-aid. This therapeutic regimen would probably be effective against limited exposure to GD and beneficial as an initial treatment for severe exposure. In addition, if the therapy were given as a prophylaxis and no exposure occurred, it should not produce any debilitating effects and the person should be able to perform the required duties.

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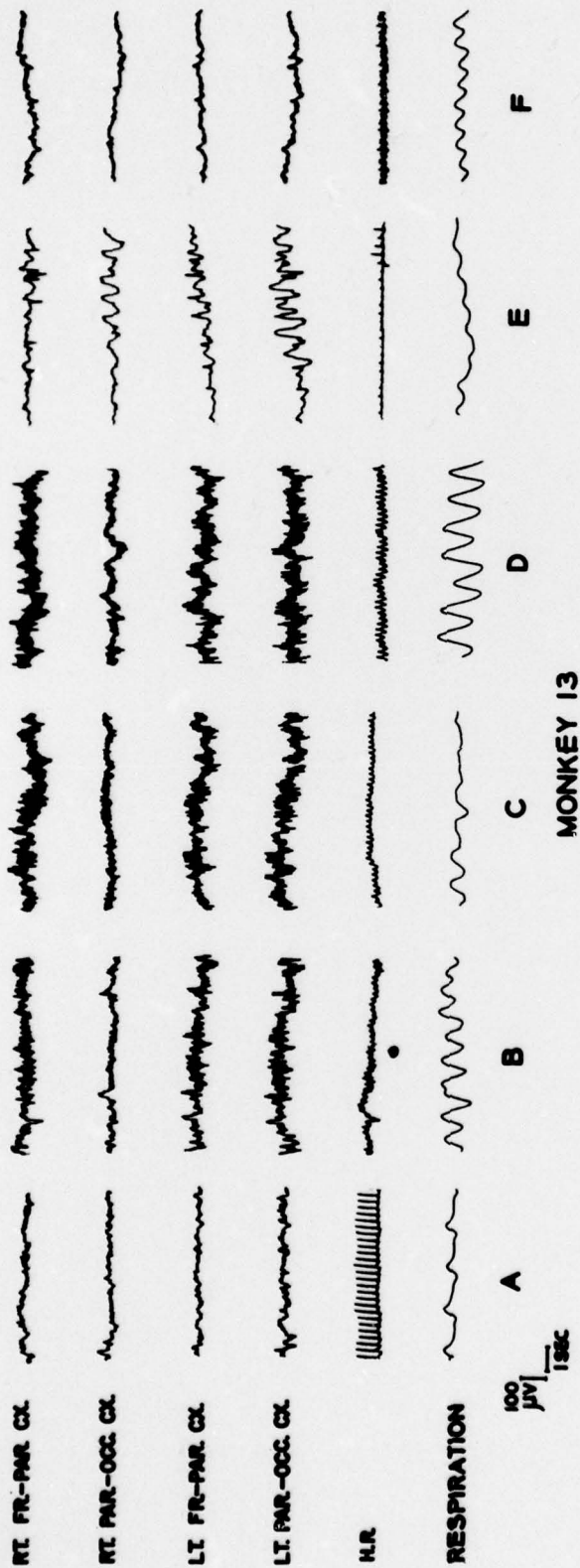


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Figure 1: Effect of GD and therapy upon EEG, heart and respiratory rate of the monkey.

- (A) Control. H.R. = 260/min; resp = 32/min.
 - (B) 15 min post GD. H.R. = 170; resp = 36.
 - (C) Immediately following administration of therapy.
H.R. = 280; resp = 48.
 - (D) 5 min post therapy. H.R. = 280; resp = 48.
 - (E) 30 min post therapy. H.R. = 230; resp = 48.
 - (F) 1 hr post therapy. H.R. = 200; resp = 52.
- Lt. Fr.-Par. Cx = Left Frontal-parietal cortex.
 Lt. Pr.-Occ. Cx = Left Parietal-occipital cortex.
 H.R. = Heart rate.

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Figure 2: EEG, heart rate and respiratory rate following exposure to GD and therapy in the monkey.

- (A) Control. H.R. = 220/min; resp = 32/min.
- (B) 10 min post GD. H.R. = 220; resp 50.
- (C) Immediately following administration of therapy.
H.R. = 260; resp = 56.
- (D) 15 min post therapy. H.R. = 250; resp = 56.
- (E) 30 min post therapy. H.R. = 120; resp = 56.
- (F) 1 hr post therapy. H.R. = 210; resp = 72.

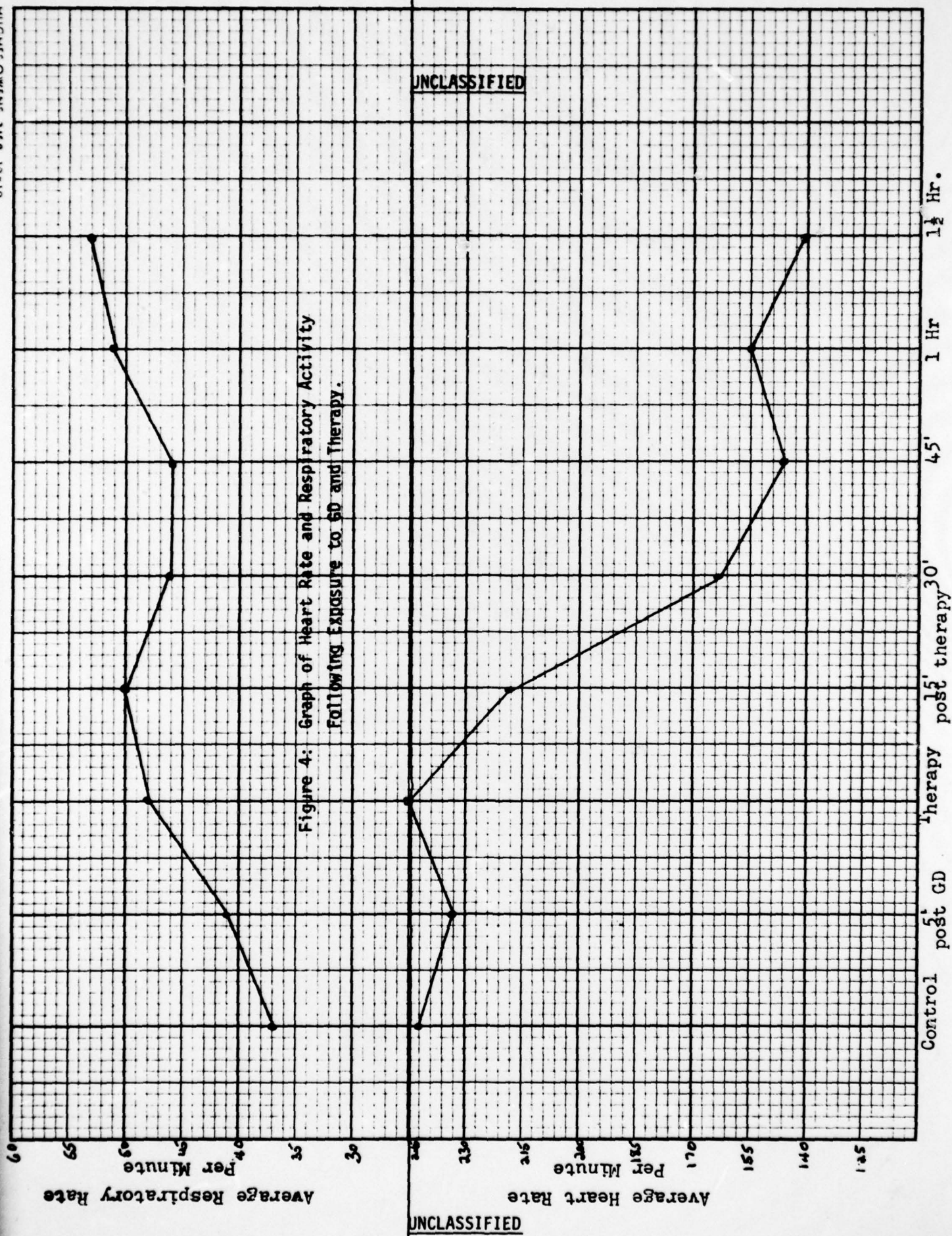
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Figure 3: Cerebral electrical activity, heart rate and respiratory rate following exposure to GD and therapy.

- (A) Control. H.R. = 240/min; resp 36/min.
- (B) 10 min post GD. H.R. = 220; resp = 36.
- (C) 5 min post therapy. H.R. = 230; resp = 40.
- (D) 15 min post therapy. H.R. = 190; resp = 40.
- (E) Monkey given additional atropine.
- (F) 30 min post therapy. H.R. = 160; resp = 36.
- (F) 1 hr post therapy. H.R. = 160; resp = 38.

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KEY WORDS

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 Clonazepam
 Atropine
 Toxogonin
 Seizure Activity
 Convulsions
 Heart Rate
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